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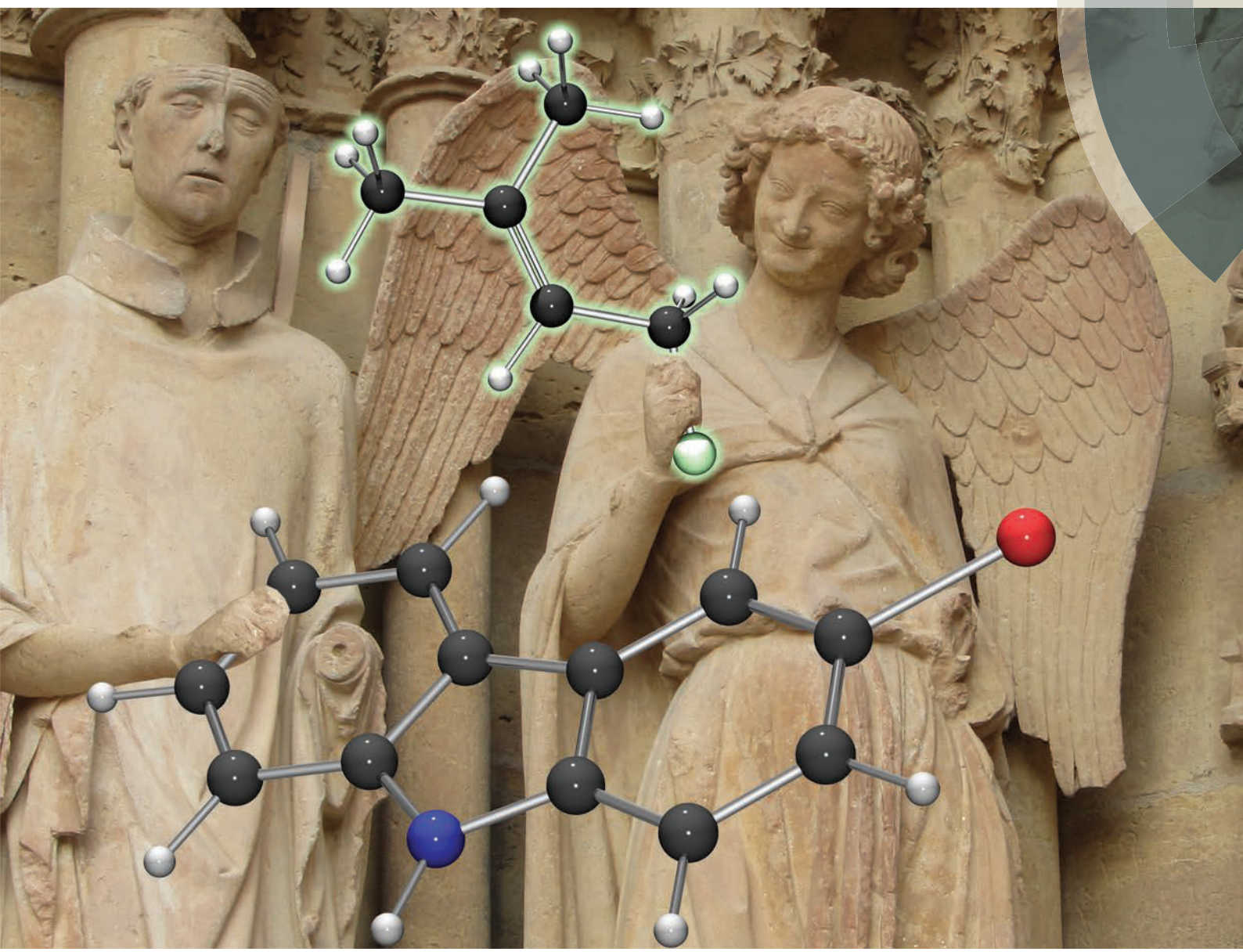

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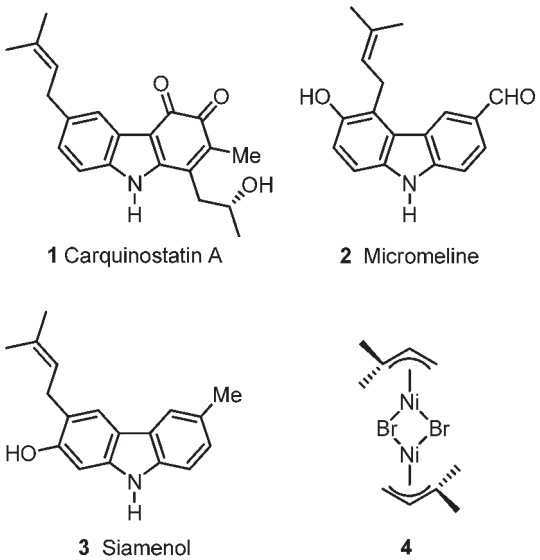
Regioselective prenylation of bromocarbazoles by palladium(0)-catalysed cross coupling – synthesis of *O*-methylsiamenol, *O*-methylmicromeline and carquinostatin A†‡

Claudia Thomas, Olga Kataeva, Arndt W. Schmidt and Hans-Joachim Knölker*

We describe the regioselective prenylation of 3-bromocarbazole by palladium(0)-catalysed cross coupling with a prenylstannane or a prenylboronate. The procedure is applied to the synthesis of precursors for biologically active carbazole alkaloids.

The prenyl (3,3-dimethylallyl) substituent is a characteristic structural feature of numerous natural products. Biosynthetically, a prenyl group is introduced by reaction with prenyl pyrophosphate, formed either by the mevalonic acid or the methylerythritol phosphate pathway.[1] Various carbazole alkaloids with a prenyl substituent have been isolated from natural sources,[2] *e.g.* the antibacterial carquinostatin A (**1**),[3] the anti-TB active micromeline (**2**)[4] and the anti-HIV active siamenol (**3**) (Fig. 1).[5]

We described the total syntheses of carquinostatin A (**1**),[6] micromeline (**2**),[7] siamenol (**3**)[8] and further prenylated carbazoles using either palladium(II)-catalysed or iron(0)-mediated reactions for construction of the carbazole skeleton.[9] Introduction of the prenyl substituent was achieved by a late-stage cross coupling of the corresponding bromocarbazole with bis[μ-bromo-(η³-1,1-dimethylallyl)nickel] (**4**). Complex **4** is readily prepared by reaction of prenyl bromide with tetracarbonylnickel and has been applied to the prenylation of alkyl and aryl halides.[10] The dimeric π-prenylnickel bromide complex **4** provides satisfactory results in the cross coupling reaction with bromocarbazoles and tolerates many functional groups including free phenolic hydroxy groups. However, the nickel complex **4** has some drawbacks: (1) highly toxic tetracarbonylnickel is used for its preparation, (2) over-stoichiometric amounts of complex **4** are required for the coupling reaction and (3) complex **4** is very sensitive to oxygen. Therefore, a range of methods has been developed for the palladium-catalysed prenylation or *tert*-prenylation of aryl and heteroaryl ring systems.[11]



1 Carquinostatin A **2** Micromeline **3** Siamenol **4**

Fig. 1 Naturally occurring prenylated carbazole alkaloids and bis[μ-bromo-(η³-1,1-dimethylallyl)nickel] (**4**).

Palladium-catalysed prenylations often lead to mixtures of products resulting from either isomerisation *via* the intermediate π-allyl–palladium complex or allyl inversion in the transmetallation step.[11,12] Herein, we report an efficient procedure for the palladium(0)-catalysed cross coupling of prenylmetal species with bromocarbazoles containing an unprotected carbazole nitrogen atom.

We selected 3-bromocarbazole (**5**) as a model compound in order to develop a general procedure for the prenylation of carbazoles (Scheme 1). The reaction of **5** with the dimeric nickel complex **4** afforded 3-prenylcarbazole (**6**) in 80–85% yield. Our first attempts to achieve a palladium(0)-catalysed Stille cross coupling of **5** and tributylprenylstannane (**8**) resulted mainly in hydrodebromination to carbazole. Screening a variety of

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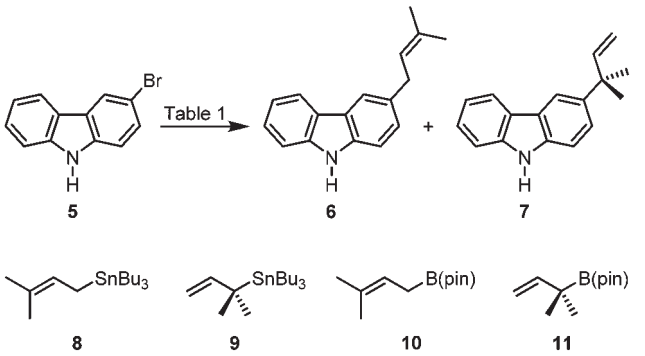
‡ Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and ^{1}H and ^{13}C NMR spectra for compounds **6**, **7**, **13**, **15** and **17**. CCDC 960617. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42297f



Scheme 1 Palladium(0)-catalysed coupling of 3-bromocarbazole (**5**) with the prenyl reagents **8**, **10** and the *tert*-prenyl reagents **9**, **11**; (pin) = pinacolato.

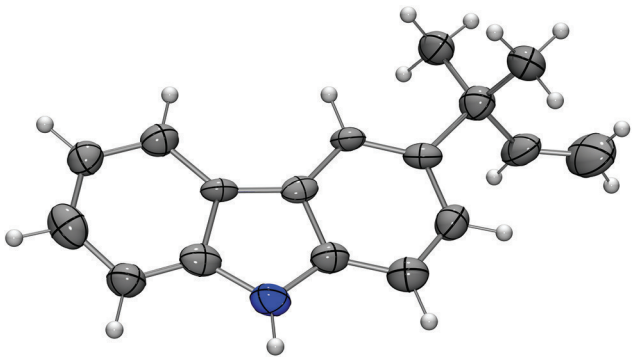


Fig. 2 Molecular structure of 3-*tert*-prenylcarbazole (**7**) in the crystal. ORTEP plot showing thermal ellipsoids at the 50% probability level.§

ligands, palladium sources and additives, we found that application of $Pd(dba)_2$ in the presence of tri-*tert*-butylphosphane and caesium fluoride (*cf.* the analogous conditions reported by Schmalz *et al.* for the prenylation of bromoarenes)[13] gave the best conversion and no detectable hydrodebromination (Table 1).

Cross coupling of the prenylstannane **8** with 3-bromocarbazole (**5**) occurred with complete inversion of the allyl system and provided 3-*tert*-prenylcarbazole (**7**). The structure of compound **7** has been unambiguously confirmed by a single crystal X-ray analysis (Fig. 2). On the other hand, coupling of the *tert*-prenylstannane **9**[14] with **5** provided the desired 3-prenylcarbazole (**6**) in 82% yield without any trace of **7** *via* inversion of the allyl system. In line with these observations, using a mixture of the prenylstannane **8** and the *tert*-prenylstannane **9** (ratio 1 : 5.9) for the cross coupling with **5** afforded a mixture of the prenylcarbazole **6** and the *tert*-prenylcarbazole **7** (ratio 5 : 1). The *tert*-prenylstannane **9** is not stable towards 1,3-isomerisation.[14,15] A thermal rearrangement of **9** to **8** can be followed over 1 h by ^{1}H NMR spectroscopy in DMF-d_7 at 80 °C. Thus, we tested the Suzuki–Miyaura coupling which has the additional advantage that toxic tin reagents are avoided.[16] The prenylboronate **10** and the *tert*-prenylboronate **11** were applied to the palladium(0)-catalysed coupling with 3-bromocarbazole (**5**) (Scheme 1, Table 1).[17] Cross coupling of the prenylboronate **10** with **5** afforded 3-*tert*-prenylcarbazole (**7**) in 89% yield by complete inversion of the allyl system. Analogously, cross coupling of the *tert*-prenylboronate **11** with **5** provided exclusively 3-prenylcarbazole (**6**).

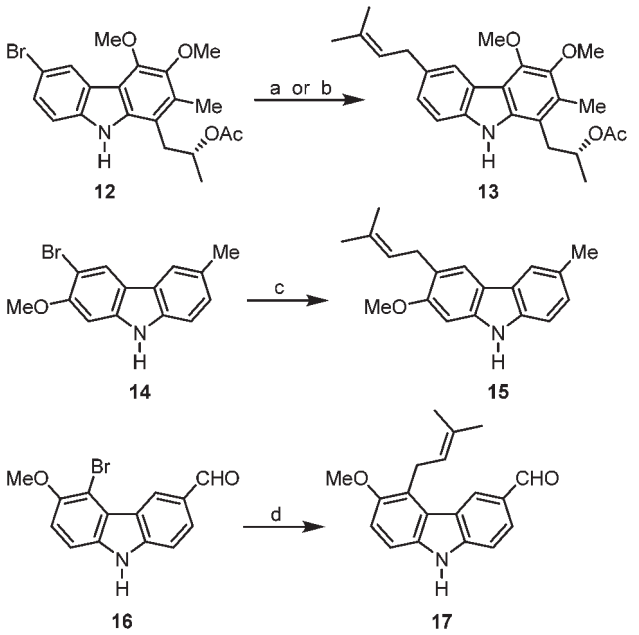
Finally, we applied the palladium(0)-catalysed prenylation to precursors for the total synthesis of biologically active carbazole alkaloids (Scheme 2). Palladium(0)-catalysed coupling of the bromocarbazole **12**[6a–c,18] with the *tert*-prenylstannane **9** or the *tert*-prenylboronate **11** provided the prenylcarbazole **13** in 78% and 85% yield, respectively. We have shown previously that compound **13** is easily converted into carquinostatin A (**1**) by removal of the acetyl group and oxidation to an *ortho*-quinone.[6a–c] Coupling of 6-bromo-7-methoxy-3-methylcarbazole (**14**)[8] and the *tert*-prenylboronate **11** provided *O*-methylsiamenol (**15**) and thus demonstrated that an *ortho*-substituent is tolerated. Due to the *peri*-interaction, coupling reactions at position 4 or 5 respectively of the carbazole skeleton can be difficult. Using the present procedure, cross coupling of 5-bromo-6-methoxycarbazole-3-carbaldehyde (**16**)[7] and the *tert*-prenylboronate **11** under optimised conditions provided *O*-methylmicromeline (**17**)[19] in 83% yield. Micromeline (**2**) and some derivatives of carbazole **12** were shown to exhibit anti-TB activity.[4,20]

In conclusion, we have described the regioselective introduction of prenyl and *tert*-prenyl groups at bromocarbazoles in high yields. Both substituents are introduced by palladium(0)-catalysed cross coupling with complete inversion of the allyl system of the corresponding stannane or boronate reagents. The methodology has been applied to the direct prenylation of precursors for biologically active carbazole alkaloids and is superior to two-step procedures involving allylation followed by olefin cross metathesis with isobutene using Grubbs II catalyst.[21]

Table 1 Reagents and conditions for the prenylation of 3-bromocarbazole (**5**)

Reagent	Reaction conditions	Ratio **6** : **7**[a]
4	5.0 equiv. $Ni(CO)_4$, 2.0 equiv. prenyl bromide, PhH, reflux, 0.5 h; then DMF, 50 °C, 2 d	1 : 0
8	10 mol% $Pd(dba)_2$, 24 mol% tBu_3P, 1.2 equiv. **8**, 1.6 equiv. CsF, DMF, rt, 24 h	0 : 1
9	10 mol% $Pd(dba)_2$, 24 mol% tBu_3P, 1.2 equiv. **9**, 1.6 equiv. CsF, DMF, rt, 24 h	1 : 0
8 + **9** (1 : 5.9)[a]	10 mol% $Pd(dba)_2$, 24 mol% tBu_3P, 1.2 equiv. **8** + **9**, 1.6 equiv. CsF, DMF, rt, 24 h	5.0 : 1
10	16 mol% $Pd(dba)_2$, 31 mol% tBu_3P, 1.5 equiv. **10**, 4.0 equiv. CsF, DMF, rt, 24 h	0 : 1
11	16 mol% $Pd(dba)_2$, 31 mol% tBu_3P, 1.5 equiv. **11**, 4.0 equiv. CsF, DMF, rt, 24 h	1 : 0

[a] Ratio as determined by NMR integration; yields: 80–90% of **6** and **7**.



Scheme 2 Synthesis of prenylated carbazoles. *Reagents and conditions*: (a) 16 mol% $Pd(dba)_2$, 36 mol% tBu_3P, 1.3 equiv. **9**, 1.2 equiv. CsF, DMF, rt, 24 h, 78%; (b) 21 mol% $Pd(dba)_2$, 42 mol% tBu_3P, 2.4 equiv. **11**, 1.1 equiv. CsF, DMF, rt, 5 d, 85%; (c) 22 mol% $Pd(dba)_2$, 42 mol% tBu_3P, 2.4 equiv. **11**, 2.5 equiv. CsF, DMF, rt, 4 d, 57%; (d) 22 mol% $Pd(dba)_2$, 40 mol% tBu_3P, 1.7 equiv. **11**, 2.2 equiv. CsF, DMF–THF (2 : 1), rt, 4 d, 83%.

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Notes and references

§ The crystals were thin plates of poor quality exhibiting static disorder, which explains the low ratio of observed reflections, poor internal consistency of the data set and its low completeness. However, the structure was determined unambiguously in the *C*2/*c* space group with three independent molecules possessing slightly different oriented C=C double bonds.

Crystal data for compound **7**: $C_{17}H_{17}N$, M = 235.32 g mol^{-1}, crystal size: 0.46 × 0.16 × 0.03 mm^3, monoclinic, space group: *C*2/*c*, a = 59.250(11), b = 5.953(2), c = 22.550(4) Å, β = 90.930(10)°, V = 7953(3) Å^3, Z = 24, ρ_{calcd} = 1.179 g cm^{-3}, μ = 0.068 mm^{-1}, λ = 0.71073 Å, T = 198(2) K, θ range = 1.37–25.00°, reflections collected: 30 780, independent: 6825 (R_{int} 0.1229), 498 parameters. The structure was solved by direct methods and refined by full-matrix least squares on F^2; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0884, wR_2 = 0.2424; maximal residual electron density: 0.323 e Å^{-3}. CCDC 960617 contains the supplementary crystallographic data for this paper.

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